

REMARKS

This case contains claims 2-5, 7-13 and 20 with the entry of the present Amendment. Claims 1 and 6 have been canceled without prejudice. Claims 3-5, 7, 9, and 10 have been amended for improved clarity. Amended claim 4 is supported by Tables 1A, 1B, and 1C in the Specification, at pages 8-10. Amended claim 5 is supported by the Specification, from line 17 at page 11 to line 9 at page 12. New claim 20 is supported by the as-filed claim 1. None of the amendments made herein constitutes the addition of new matter.

The Rejection under 35 U.S.C. 112:

Claims 1-12 are rejected under 35 U.S.C. 112, first paragraph, on the grounds that the specification, while enabling for a method of identifying the metastatic potential of a prostate cancer cell line expressing the gene encoding MUC18, does not reasonably provide enablement for a method of identifying the metastatic potential of any prostate cancer that does not express the gene encoding MUC18. Therefore, the specification does not enable any person skilled in the art to which it pertains to make and/or use the invention commensurate in scope with these claims. Applicants respectfully traverse this rejection.

Without acquiescing to the rejection and in the interest of advancing the prosecution of this case, claim 20 (amended version of the as-filed claim 1) recites specifically, "a method for identifying metastatic potential of a prostate cancer cell expressing the gene encoding MUC18....". Therefore, the allegation that the specification does not reasonably provide enablement for a method of identifying the metastatic potential of any prostate cancer that does not express the gene encoding MUC18, is no longer applicable. Withdrawal of the rejection under 35 U.S.C. 112, first paragraph, is respectfully requested.

It is further stated:

There is an uncertainty that every tumor biopsy from each different patient, though diagnosed with the same type of metastatic cancer, will test positive for MUC18 expression. As a consequence, the results of an analysis according to the claimed method may be highly undesirable.

Applicants point out that the claimed method as amended is designed to be used to identify metastatic potential only when a prostate cancer cell expresses the higher level of the MUC18 gene than the normal prostate cell. Thus, the metastatic potential is identified by the results of the analyses according to the claimed method. If a given sample does not express the gene encoding MUC18, the claimed method is not applicable in such a case.

The Examiner alleges:

Thus, there is obviously not a foregoing assumption that metastatic cancer will express MUC18. More importantly, with regard to the instant application, it cannot be presumed that, if a cancer cell does not express MUC18 it does not have the potential to metastasize, or even that it is not already metastatic.

The present application does not teach that if a cancer cell does not express MUC18 it does not have the potential to metastasize, or even that it is not already metastatic. Instead, claim 20 (amended version of the as-filed claim 1) teaches that the claimed method is applicable if a prostate cancer cell expresses the gene encoding MUC18 higher level than a normal prostate cell, the prostate cancer cell is likely to have metastatic potential. The above-assumption alleged by the Examiner stems from reading into the meaning of the claim language which is beyond the scope of the claims. The metes and bounds of Claim 20 as recited are definite and clear. A person of ordinary skill in the art would understand what is intended by the claim language.

The Examiner asserts that the teachings of Filshie et al. and Shih et al. indicate that MUC18 positivity cannot be used as the sole criterion for establishing whether or not a cancer

cell has the potential to metastasize. This allegation is based on Filshie et al.'s finding that one of five B cell lines and one of four myeloid lines express MUC18 and Shih et al.'s finding that not all the mesenchymal neoplasms express the MUC18 gene.

Filshie et al. reported that the MUC18 gene is not expressed on bone marrow stromal cells. Furthermore, it is stated in Filshie et al., "One out of three cases of T-ALL, four out of twenty cases of B lineage ALL (mainly precursor-B and pre-B phenotype), two out of seven with AML and were found to react with the antibodies. The percentage of positive cells as well as the intensity of staining varied considerably between cases, with no particular pattern emerging" (emphasis added). See from the last paragraph in column 1 to the top of column 2. Therefore, the findings of the cited reference do not serve as suggestion or motivation for one skilled in the art to make the claimed invention. Shih et al. found that the MUC18 gene is expressed in a wide variety of mesenchymal neoplasms. Thus, the teachings of Filshie et al. and Shih et al. have little relevance to the present invention. The expression of the MUC18 gene is expected to vary depending on the cell types analyzed. The claimed invention specifically defines the MUC18 expression in a prostate cancer cell and its utility in predicting metastatic potential according to its expression level. Therefore, the allegation by the Examiner is not justified in the present case.

The Patent Office states:

The teachings of the Specification are inaccurate. Because U.S. Patent 6184043 B1 teaches that the metastatic cancer cell line DU-145 does not express the MUC18 polypeptide. This discrepancy suggests a need for further experimentation. It is noted that apart from the analysis of four prostate cancer cell lines, the specification teaches the result of an analysis of a single patient biopsy.....The data are insufficient to establish clinical or experimental significance.....one skilled in the art cannot practice the invention in a clinical setting without further undue experimentation to determine if, indeed, there is experimental and clinical significance, which would provide the artisan with a reasonable expectation of success.

The present invention provides an improved prognostic test for a prostate cancer with a relatively high potential for metastasis. The claimed method for identifying metastatic potential of a prostate cancer cell is based on the key finding that when a non-metastatic human prostate cancer cell line (LNCAP), which does not express the gene encoding MUC18 was transfected with the human MUC18 coding sequence, it became metastatic (see Specification at page 13, lines 14-29, and also Example 1, from page 17, line 13 to Example 2, page 19, line 26). Therefore, the allegation that the claimed invention was made based solely on the studies on four cell lines and a sample from a primary prostate cancer tissue is not correct. The demonstration that the expression of the introduced MUC18 gene into a non-metastatic cancer cell converted these cells into metastatic cancer cells demonstrates that the MUC18 gene plays a critical role in cancer metastasis, and thus provides the basis for using the MUC18 expression level to predict metastatic potential of a prostate cancer cell.

With respect to the discrepancy in the expression of MUC18 in the DU-145 cell, it is likely due to the difference in the sensitivity of different detection methods. The results of the present application were obtained by employing Northern and Western analyses while the '043 patent used immunomagnetic detection method to measure the level of MUC18 expression. This type of discrepancy is well known to a person of ordinary skill in the art. The most relevant data for the claimed invention are the results by the inventors demonstrating that when the MUC18 gene was introduced to the DU-145 cells, these cells became metastatic. These results establish the importance of the MUC18 gene expression for metastasis in prostate cancer cells and thus support the claimed methods.

Claims 1-5 are further rejected under 35 U.S.C. 112, first paragraph, because the Specification, while being enabled for a method of identifying the metastatic potential of a prostate cancer cell line that expresses the gene encoding the MUC18 polypeptide (SEQ ID NO:2) using an antibody capable of specific binding to the middle portion of the MUC18 polypeptide, which spans amino acid residues 631-1128 of SEQ ID NO:2, does not reasonably provide enablement for a method of identifying the metastatic potential of a prostate cancer cell

that does not express the gene encoding MUC18 using any antibody made in an experimental laboratory animal in response to a MUC18 antigen.

Without acquiescing to this rejection and in the interest of advancing the prosecution of this case, claims 3- 5 have been amended for improved clarity. Amended claim 4 recites an additional limitation of the MUC18 amino acid sequence as shown in SEQ ID NO:2. Amended claim 5 recites specific amino acid sequence defining the middle portion of the MUC18 antigen (amino acid residues 211-376 of SEQ ID NO:2). In addition, new claim 20, which is the amended version of the as-filed claim 1, defines the method applicable only for prostate cancer cells which express the gene encoding MUC18. The claimed method is not applicable if a prostate cancer cell does not express the gene encoding MUC18. Claims 3-5 are dependent claims of claim 20. If an independent claim (e.g. claim 20) is considered to be allowable, dependent claims should in turn be allowable. The Specification provides a detailed description of how the antibodies were generated and used in determining the levels of MUC18 expression in western blot analysis as shown in Figures 6 and 7, and Examples 1 and 4 (see pages 16-17, and pages 21-22 of the Specification). Therefore, the allegation that the teachings of the Specification cannot be extrapolated to the enablement of the invention commensurate in scope with the claims is no longer applicable.

The Rejection under 35 U.S.C. 112, second paragraph:

Claims 1-12 are rejected under 35 U.S.C. 112, second paragraph, as indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants respectfully traverse this rejection.

Without acquiescing to the rejection and in the interest of advancing the prosecution of this case, claim 1 has been canceled without prejudice. Claim 20, which replaces as-filed claim 1, has limitations suggested by the Examiner.

Claims 1-12 are alleged to be vague and indefinite based on the use of a phrase, "metastatic potential" because this term is not defined in the Specification and it cannot be ascertained what specific properties of a prostate cancer cell define the claimed potential for metastasis.

Applicants point out that the meaning of the term, metastatic potential, in claim 20 (i.e., amended claim 1), is intended to mean what is readily understood by a person of ordinary skill in the art. "Metastasis" is defined as the shifting of a disease or its local manifestations, from one part of the body to another.... And the term, "potential", is defined as capable of doing or being, although not yet doing or being, possible but not actual in the Stedman's Medical Dictionary (26th Edition, Williams & Wilkins, Baltimore, A Waverly Company). The meaning of metastatic potential used in claim 20 is exactly as that defined in the Medical Dictionary. Furthermore, claim 20 defines a method of identifying metastatic potential by comparing the levels of MUC18 expression between a prostate cancer cell expressing the gene encoding MUC18 and a normal prostate cell. If certain prostate cancer cells express higher levels of MUC18 gene than normal prostate cells, they are identified as having metastatic potential. Therefore, expressing higher level of MUC18 is one criterion of a cancer cell for having metastatic potential.

Applicants further point out that the metastatic potential as recited in the claims is used synonymously with the term "metastatic ability" in the present application. Example 2 at page 18 in the Specification provides detailed protocol of how to determine metastatic abilities such as the degree of motility and the invasiveness of prostate cancer cells. The results described confirm that the relative levels of MUC18 expression in prostate cancer cells correlate positively with metastatic ability, i.e., metastatic potential. Based on the foregoing, it is submitted that the meaning of the term, metastatic potential, is abundantly clear and definite.

The Rejection under 35 U.S.C. 102:

Claims 1-5 are rejected under 35 U.S.C. 102(b) as anticipated by Rubenstein et al. (Prostate 14: 383-388, 1989), as evidenced by Shih et al. (Cancer Research 54:2514-2520, 1994), Liu et al. (Hinyokika Kyo Acta Urologica Japonica 39: 439-444, 1993), and the annotation that accompanies the MUC18 amino acid sequence entry (Accession No. P43121) in the Swiss Protein Database. Applicants respectfully traverse this rejection.

The Office Action states:

Rubenstein et al. teaches an immunohistologic method for assessing the metastatic potential of prostate cancer cells. Specifically, Rubenstein et al. teaches that the method can be used to distinguish benign prostate tissue and malignant prostate tissue. The method of Rubenstein et al. comprises the detection and enumeration of more than one tumor-associated antigen or marker on the surface of metastatic prostate cells. One of the antigens that is detected in the immunoassay of Rubenstein et al. is also known to be a natural killer (NK) cell marker, which Rubenstein et al. refers to as Leu-7. The Leu-7 antigen is also known as the HNK-1 antigen, as evidenced by Liu et al. The HNK-1/Leu-7 antigen is an epitope of the melanoma-associated antigen A32, which is identical to MUC18, as evidenced by Shih et al. Therefore, the anti-HNK-1 antibody that is used by Rubenstein et al. to identify prostate cancer cells that have the potential to metastasize anticipates the anti-MUC18 antibody that is used in the claimed invention.

Applicants point out that the Rubenstein reference teaches how to apply the immunohistologic staining to develop a malignant index (MI) to aid in distinguishing benign from malignant prostate tissue. The malignant index was determined based on the reactivity of several commercially available antibodies against certain antigens on a scale of 0-5 in a given tissue. One of the antibodies used was Leu-7. The Leu-7 antigen is an epitope in the MUC18 polypeptide. However, the value of Leu-7 immunoreactivity used to determine MI in the cited reference was obtained from the mononuclear cell staining rather than that of the prostatic epithelium (see page 386, third to fifth lines under the Results heading). Therefore, these studies do not provide any connection between the level of the MUC18 expression and metastasis of

prostate cancer cells. The conclusions made in the cited reference are based on the expression level of MUC18 in mononuclear cells. Nothing in the cited reference provides guidance in determining the role of Leu-7 (i.e., MUC18) in assessing the metastatic potential of prostate cancer cells, contrary to the allegation by the Patent Office. By contrast, the claimed invention is a method for identifying metastatic potential for a prostate cancer cell by measuring the level of expression of the MUC18 gene directly either at the transcriptional or translational level. Therefore, the claimed invention is distinct from the method taught by Rubenstein et al. Withdrawal of the rejection under 35 U.S.C. 102 is respectfully requested.

The Rejection under 35 U.S.C. 103:

Claims 1-12 are rejected under 35 U.S.C. 103(a) as unpatentable over Rubenstein et al., in view of Liu et al., Shih et al., and in further view of U.S. Patent No. 6,057,105A, as evidenced by the annotation that accompanies the MUC18 amino acid sequence entry in the Swiss Protein Database. Applicants respectfully traverse this rejection.

The shortcomings of the Rubenstein reference have been discussed above. Rubenstein et al. does not teach the use of the anti-MUC18 antibody as taught in the present application. Rubenstein et al. does not teach the use of a prostate cancer cell line, nor does it teach the detection methods such as Northern hybridization and RT-PCR.

Liu et al. is alleged to teach that the Leu-7 detected in the immunoassay of Rubenstein et al. is also known as the HNK-1 antigen and that the expression of the HNK-1 antigen in prostate cancer cells may be a useful prognostic factor in patients with prostate cancer. Liu et al. is further alleged to teach that, of the 52 patients with prostate cancer, 49 patients (94%) showed reactivity to anti-HNK-1 Mab and the immunoreaction was associated with the histological differentiation of prostate cancer.

Contrary to the Examiner's allegation, Liu et al. teaches the opposite of what the claimed invention teaches; longer survival times and interval free of progression were observed in

prostate cancer patients showing higher HNK-1 expression (e.g., Leu-7, an epitope of MUC18) and patients showing decreased HNK-1 expression had a less favorable outcome (see Abstract, lines 13-16 and right column of page 442 in Discussion). In contrast, the claimed method is to identify metastatic potential when a prostate cancer cell expresses higher level of the MUC18 gene than a normal prostate cell. Thus, one of ordinary skill in the art could not have derived any motivation from the Liu et al. reference to make the claimed invention. If any, Liu et al. teaches a skilled artisan away from making the claimed invention.

Shih et al. is alleged to teach that the HNK-1/Leu-7 antigen is an epitope of the melanoma-associated antigen A32 and the A32 antigen showed sequence identity to the MUC18 antigen. Shih et al. further teach that melanoma cells express three additional members of the immunoglobulin supergene family, i.e., vascular CAM, N-CAM, and MUC18 antigen, and the MUC18 expression correlates significantly with metastatic potential.

Applicants respectfully submit that Shih et al. does not even mention prostate cancer. The cited reference describes the profile of Mel-CAM (e.g., MUC18) expression by immunochemistry using a Mel-CAM-specific polyclonal antibody in a variety of mesenchymal neoplasms. Their results showed that Mel-CAM is expressed consistently in neoplasms of smooth muscle and vascular origin and that Mel-CAM may be a potential modulator of malignant transformation in peripheral nerve tumors. However, Shih et al. stated that "Mel-CAM is expressed strongly in nonneoplastic smooth muscle and vascular endothelium, it is thus difficult to know whether Mel-CAM expression is involved in the progression of smooth muscle or vascular tumors." (See page 574, midsection of the left column). Therefore, nothing in Shih et al. provides or suggests a link between MUC18 expression and prostate cancer.

U.S. Patent No. 5,807,978A ('978 patent) is alleged to teach a method for identifying peptides derived from prostate tumor-associated antigens that correspond to the immunodominant epitopes found in the native antigens, which can be used to produce reagent antibodies that are capable of specifically binding said antigens for use in diagnostic assays. It is

further alleged that, in theory, the application of the immunological model described in the patent could be applied to practically any polypeptide, i.e., the invention can be used to generate an anti-MUC18 antibody.

Applicants argue that the '978 patent describes the immunogenic peptides of prostate specific antigen (PSA). There is no teaching or suggestion of MUC18 in the cited patent. Nothing in the cited patent suggests that the invention described therein can be applied to MUC18. Unless the '978 patent provides motivation to one skilled in the art to make the claimed invention based on the disclosure of the cited patent, a skilled artisan would not have been motivated to apply the teachings of the '978 patent to the MUC18 polypeptide. A rejection for obviousness cannot be based on hindsight. See ACS Hospital Systems, Inc. v. Montfore Hospital, Inc., 221, USPQ 929, CAFC 1984; *In re Jones* 21 USPQ 2d 1941 (Fed. Cir. 1992).

U.S. Patent No. 6,057,105A ('105 patent) is alleged to teach methods for detecting melanoma cells that have metastatic potential by detecting the level of expression of the gene encoding MUC18 by quantitative RT-PCR analysis.

The '105 patent teaches methods applicable for melanoma and breast cancer cells. The present invention relates to prostate cancer. There is no teaching or suggestion that the expression of the MUC18 gene is involved in metastasis of prostate cancer. Therefore, the cited patent provides no motivation to one skilled in the art to make the claimed invention.

The Patent Office alleges that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to make the claimed invention by combining the cited references. Applicants do not agree with this allegation.

A rejection for obviousness over a combination of references cannot be sustained unless motivation to combine the teachings can be found within the references themselves. *In re Jones*, 21USPQ2d 1941 (Fed. Cir. 1992) ("Before the PTO may combine the disclosures of two or more

prior art references in order to establish prima facie obviousness, there must be some suggestion for doing so, found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art.”). None of the cited references provide such motivation. Rubenstein et al. used the value for the Leu-7 in calculating the MI from the mononuclear cell staining, not from the prostate cancer tissue. Therefore, the teachings of Rubenstein et al. have little relevance to the claimed invention of the present application. Liu et al. does not cure the deficiencies of Rubenstein et al. As discussed above, Liu et al. describes the opposite of the claimed invention and thus teaches one skilled in the art away from making the claimed invention. Shih et al. simply reports the profile of MUC18 expression in a variety of mesenchymal neoplasms. There is no mention of prostate cancer in the Shih et al. reference. The '978 patent discloses immunogenic peptides derived from prostate specific antigen (PSA) and their use in diagnostic assays. Nothing in the '978 patent suggests the use of MUC18 for identifying metastatic potential in prostate cancer. The '105 patent discloses methods for detecting metastasis of melanoma and breast cancer by measuring the levels of MUC18 expression. Nothing in this patent suggests the use of MUC18 expression levels for the same purpose in prostate cancer. Accordingly, none of the cited references, singly or in combination, provide motivation to one skilled in the art to make the claimed invention. Therefore, the rejection under 35 U.S.C. 103 is not justified and withdrawal is respectfully requested.

Conclusion:

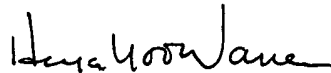
Based on the foregoing, this case is considered to be in condition for allowance and passage to issuance is respectfully requested.

If there are any outstanding issues related to patentability, the courtesy of a telephone interview is requested, and the Examiner is invited to call to arrange a mutually convenient time.

This Amendment is accompanied by a Petition for Extension of Time (two months) and a check in the amount of \$195.00 as required under 37 C.F.R. 1.17(a)(3) for a small entity. If the

amount submitted is incorrect, however, please charge any deficiency or credit any overpayment to Deposit Account No. 07-1969.

Respectfully submitted,

A handwritten signature in black ink, appearing to read 'Heeja Yoo-Warren'.

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US Serial No: 09/653,961

Amended Claims - Version with markings to show changes made.

3. (Once amended) The method of claim 20 [1], wherein expression of the [a] MUC18 coding sequence is determined by immunoassay.
4. (Once amended) The method of claim 3, wherein expression of the MUC18 coding sequence is determined by immunoassay using antibody made in an experimental laboratory animal in response to the [a] MUC18 antigen consisting of the amino acid sequence set forth in SEQ ID NO:2.
5. (Once amended) The method of claim 4, wherein the MUC18 antigen is a middle portion of the MUC18 coding sequence consisting of the amino acid sequence as set forth amino acid residues 211-376 of SEQ ID NO:2.
7. (Once amended) The method of claim 20 [1], wherein expression of the [a] MUC18 coding sequence is determined by Northern hybridization.
9. (Once amended) The method of claim 8, wherein [a] the probe used in Northern hybridization comprises a nucleotide sequence as given in SEQ ID NO:7, SEQ ID NO:9, or SEQ ID NO:10.
10. (Once amended) The method of claim 20 [1], wherein said expression of the [a] MUC18 coding sequence is determined by a reverse transcriptase-polymerase chain reaction.